

## REMARKS

Applicant gratefully acknowledges the courtesies extended by Examiner Mondesi to his representative in a May 11, 2006 telephone conference relating to the issue of trademarks appearing in the application specification. The specification is amended to indicate references to trademarks using capital letters as suggested by the Examiner.

Withdrawn claims 4, 5 and 13-20 have been canceled. New claims 21-26 correspond to original claims 6-12, but depend from claim 3. Claim 1 is amended to clarify the situation where  $m=0$  and to clarify antecedent basis. Language is based on the original claim language. Claims 2 and 3 are amended to decrease the number of members of Markush style groups. No issue of new matter arises.

### **Restriction/Election**

Withdrawn claims have been canceled.

### **Rejections under 35 U.S.C. §112, first paragraph**

At page 4, last paragraph, the Office action rejected claim 1 (and dependent claims 2, 3 and 6-12) as allegedly lacking written description. Applicant respectfully traverses this rejection.

The specification exemplifies several signal sequences. See e.g., Examples 1-3. The Office action acknowledges additional signal sequences are known in the art. The signal sequence has the known function of directing the associated protein for secretion. Regardless of the species or specific structure, so long as the signal sequence has the function of a signal sequence, i.e., it acts as a signal sequence, it is suitable for the present invention. Since the species of the signal sequence is irrelevant so long as the signal sequence functions as a signal sequence, no more description than "signal sequence" is necessary. The Office action does not provide any rationale why even one species of signal sequence is necessary for the written description requirement, let alone a recitation of all examples known. The three examples cited in the Office action are more than sufficient to be representative of all species of signal sequence. Reconsideration and withdrawal of this rejection are respectfully requested.

At page 6, claims 1-3 and 6-12 were rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. Applicant respectfully traverses this rejection.

At page 7, part 1-2, the breadth and nature of the claimed invention are discussed. The Invention is alleged to "encompass a broad number of nucleic acid sequences". Applicant does not deny this allegation. This aspect of the rejection asserted that the scope was not commensurate with regard to the extremely large number of promoters. Applicant respectfully traverses this aspect of the rejection. Although the number of promoters might be large, there is

no undue experimentation required to use any selected promoter to effect transcription and eventual expression. The Office action provided no theory why any promoter would be unsuitable or any indication of numbers of unsuitable promoters that would give rise to a requirement for undue experimentation. Reconsideration and withdrawal of this aspect of the rejection are respectfully requested.

At page 8, part 3, the state of prior art is discussed. A reference from 1991 is cited relating to surprising effects from mutating even a single amino acid in a protein. Although the Office action acknowledges that the reference teachings are dated, the Office action suggests that to date certainty in predicting all effects of a mutation is not the state of the art. Applicant respectfully traverse this aspect of the rejection.

Certainty of mutation effect is not a feature of the claimed invention. One featured utility is the production of pharmaceutically relevant proteins of high purity. See, e.g., paragraph [002]. Predictability of all functions relating to every mutated version of all (or any) protein(s) is not a claimed effect. Thus the invention can be practiced without perfect predictability of designed mutations. Reconsideration and withdrawal of this aspect of the rejection are respectfully requested.

At page 8, part 4, the Office action asserts the level of skill in the art, at least with respect to the method of the invention as an M.D. or Ph. D. level individual. While in the future some refinement of the training of the individual might be warranted, Applicant does not at this time believe that such is necessary at this time to resolve the pending issues.

At page 9, part 5, the level of predictability in the art is discussed. Specifically, the level of unpredictability of derivatives is discussed. Applicant respectfully traverses this aspect of the rejection.

The skilled artisan requires no undue experimentation to practice the invention as claimed. For example, even with multiple amino acid substitutions the skilled artisan is capable of recognizing conservative vs. radical substitution and the expected degree of effect of each. Furthermore, the skilled artisan is capable of recognizing active recognition amino acids and active clefts and structural portions of the protein and thus is capable of choosing functional derivatives without undue experimentation.

As an aside, Applicant notes that the claims as amended do not recite "derivatives". Thus this aspect of the rejection appears moot.

Reconsideration and withdrawal of this aspect of the rejection are respectfully requested.

At page 9, parts 6 and 7, the amount of guidance and presence of working examples are discussed. The guidance regarding additional signal sequences in the application provided in association with the three working examples cited in the Office action, is alleged to be inadequate. Applicant respectfully traverses this aspect of the rejection.

Applicant respectfully asserts that the specification is not required to disclose all related art. The skilled artisan is expected to possess skills, such as reading a disclosure of a signal sequence and judging whether to use that signal sequence, for example to practice the presently claimed invention. Thus all signal sequences are enabled, either by disclosure in the application or disclosure in literature or the art. Reconsideration and withdrawal of this aspect of the rejection are respectfully requested.

At page 10, part 8, quantity of experimentation necessary to practice the invention is discussed. The Office action asserts that it is not routine “to screen for all proteins having a substantial number of modifications having any function, as encompassed in the instant claims.” Applicant respectfully traverses this rejection.

Applicant respectfully asserts that the invention as claimed is not directed to screening for proteins having “any function”. The claimed invention features a nucleic acid construct that improves active yield of pure pharmaceutically relevant proteins. The structure of the nucleic acid of claim 1 includes a portion “Y” that is more efficiently expressed when used in the context of the present invention. The skilled artisan requires no undue experimentation to select a pharmaceutically relevant protein and to incorporate the relevant nucleic acid sequence in the nucleic acid of the present invention. Selection of a pharmaceutically active protein is within the skill of the art requiring no undue experimentation; selecting a nucleic acid encoding the protein requires no undue experimentation; constructing a nucleic acid according to the claimed invention that includes the selected nucleic acid encoding the protein likewise is accomplished without undue experimentation. **No undue experimentation is required at any stage of use of the present invention.** Thus enablement is not an issue. Reconsideration and withdrawal of this rejection are respectfully requested.

At page 11, claims 2 and 3 were rejected as allegedly being indefinite in the recitation of “derivatives”. The claims are amended to obviate this issue. Reconsideration and withdrawal of this rejection are respectfully requested.

#### **Rejection under 35 U.S.C. §103**

At page 11, claims 1-3 and 6-12 were rejected under 35 U.S.C. §103 as allegedly being obvious over Dawson in view of Price. Applicants respectfully traverse this rejection.

Dawson is cited as teaching a hirudin fusion protein. Example 1 is cited for a teaching of an alpha factor – a SLDKR linker – an hirudin – an IEGR linker – a second hirudin or a streptokinase – and a yeast PGK terminator. The Office action acknowledges that Dawson does not teach a nucleic acid with an ADH2 promoter and an alpha factor leader sequence.

Price is cited for a teaching of a nucleic acid with an ADH2 receptor and a signal sequence.

The Office action sums up the rejection by asserting that it would have been obvious to use a vector with yeast ADH2 promoter and an alpha factor leader sequence to arrive at an expression vector that encoded an hirudin – hirudin fusion protein. Applicant respectfully traverses this rejection.

The references cited in the Office action fail to teach all the claim limitations. Accordingly, no *prima facie* case of obviousness has been established. See MPEP § 2143.<sup>1</sup>

For example, whereas the Dawson reference is cited as teaching an IEGR linker is the position corresponding to the first  $Z_1Z_2$ , and the “R” can be read as corresponding to  $Z_2$ ;  $Z_1$  in the instant claim 1 is a K or R and thus cannot be considered taught or suggested by the IEG sequence of Dawson. For at least this reasons Applicant respectfully asserts that no *prima facie* case of obviousness has been established. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim 3 is patentable over the applied references for at least the same reasons that claim 1 is patentable. In addition, the subject matter of claim 3, featuring proinsulin, etc. is a further example of a feature not taught or suggested in the cited references. The cited references do not teach or suggest the subject matter recited in claim 3. Applicant respectfully asserts that had a *prima facie* case of obviousness been established claim 3 would be patentable over the applied art for at least an additional reason of unexpected results. The improved yield that results from the present invention would be sufficient to overcome a *prima facie* case of obviousness.

For at least these additional reasons with respect to claim 3 and claims 21-26 ultimately dependent therefrom, reconsideration and withdrawal of this rejection under 35 U.S.C. §103 are respectfully requested.

---

<sup>1</sup> MPEP §2143. Basic Requirements of a *Prima Facie* Case of Obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

### **Provisional Double Patenting Rejections**

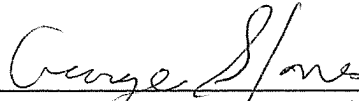
Claim 1 was provisionally rejected over a '634 application; claim 2 was provisionally rejected over a '632 application. Applicant gratefully acknowledges the Examiner's notice of this issue and will take appropriate action if and when indication of allowable claimed subject matter requires amendment or other action in the conflicting applications.

### **Conclusion**

In view of the above amendments and remarks, Applicant respectfully submits that the application is now in condition for allowance and requests prompt issuance of a Notice of Allowance. Should the Examiner believe that anything further is desirable that might put the application in even better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below.

The Commissioner is authorized to charge any additional fees or credit any overpayment necessitated by this response to Deposit Account No. 18-1982.

Respectfully submitted,



---

George S. Jones, Reg. No. 38,508  
Attorney/Agent for Applicant

sanofi-aventis U.S. LLC  
Patent Department  
Route #202-206 / P.O. Box 6800  
Bridgewater, NJ 08807-0800  
Telephone (908) 231-3776  
Telefax (908) 231-2626

Aventis Docket No. DEAV2001/0007 US NP